cc:Mail for: Kathy Allen

Subject: CLL STUDY
Forwarded: Connie Matsui 8/22/95 11:10 AM
To: Kathy Allen

FYI,

Connie

Subject: CLL STUDY
From: Antonio Grillo-Lopez
Date: 8/22/95 11:05 AM

I DISCUSSED THE CLL STUDY WITH CURD AND HELLMAN FOLLOWING THE LAST MEETING (Y2B8) WITH GNE. THEY WILL DO THE STUDY IN THE US IN THE SITES WE PROPOSED AND WILL DVELOP A PROTOCOL WITH US. THEY STILL DON'T HAVE "BUY IN" FROM GNE MANAGEMENT BUT ARE PROCEEDING WITH THE EXPECTATION IT WILL BE APPROVED. IN THE PAST, TONY MAN HAS TOLD ME HE PREFERS FOR THIS STUDY TO BE DONE IN THE US.

SEE MY LAST COMMUNICATIONS BELOW.

ANTONIO
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DEAR SUE,

THANK YOU FOR YOUR MESSAGE SUMMARIZING OUR DISCUSSION ON THE DESIGN OF THE CLL STUDY.

HERE ARE SOME COMMENTS:

A. DLTs- ONLY IF PERSISTENT AFTER TEMPORARILY STOPPING THE INFUSION OR IF INFUSION CANNOT BE RESTARTED/COMPLETED AFTERWARDS- AND:
1. BRONCHOSPASM NOT RELIEVED BY NASAL O2, AND/OR BRONCHODILATORS (INHALER). IF IV BRONCHODILATORS ARE REQUIRED OR IF THERE IS DYSPNEA AT NORMAL LEVEL OF ACTIVITY, THIS WOULD BE GRADE 3 AND CONSTITUTE DLT. LIKEWISE FOR STEROIDS.
2. HYPOTENSION IF GRADE 3.
3. ANGIOEDEMA IF PART OF A GRADE 3 ALLERGIC REACTION.

B. CASE REPORT FORMS-
1. A SET IS BEING MAILED TO YOU/JOHN
2. AN INSTRUCTIONS MANUAL FOR CRFs LIKEWISE

C. WE WILL NEED TO WORK OUT HOW ADVERSE EVENTS WILL BE REPORTED TO US SO THAT WE CAN COMPLY WITH 3 DAY PHONE AND 10 DAY WRITTEN REPORT REQUIREMENTS AS WELL AS OTHER REPORTING RESPONSIBILITIES UNDER THE IDBC IND.

D. WE WILL NEED TO WORK OUT HOW THE DATA WILL FLOW TO OUR DATA BASE AND REPORTS GENERATED. DATA FROM THIS STUDY WILL HAVE TO BE INCORPORATED IN OUR PLA (STUDY REPORT, INTEGRATED SUMMARIES EFFICACY/SAFETY, ETC.).

E. I WILL SEND YOU COPY OF OUR SAMPLE INFORMED CONSENT AND OF OUR CLINICAL TRIALS AGREEMENT. I KNOW YOU HAVE YOUR OWN BUT IT MAY BE USEFUL TO SEE HOW WE HAVE DEALT WITH ISSUES SPECIFIC TO THESE STUDIES AND TO INFORM YOU ABOUT SOME OF OUR PROCEDURES. YOUR CALL AS TO HOW ALL OF THIS WILL BE HANDLED.

PLEASE LET ME KNOW HOW I CAN BE OF ASSISTANCE OR IF YOU NEED ANY FURTHER INFORMATION THAT I CAN SUPPLY. I LOOK FORWARD TO WORKING WITH YOU AND JOHN ON

THIS STUDY.

BEST REGARDS,
ANTONIO

FYI.
ANTONIO

Subject: Re: GNE - IDEC MEETING
From: desmond@GENE.COM at Internet
Date: 8/15/95 9:44 PM

Dear Antonio,=20

I received your e-mail. Thanks to you and your colleagues for an extremely productive day. I think it would be useful to summarize the major thoughts regarding the CLL study synopsis which came out of our meeting today:

Study design: Phase Ib/IIa dose-ranging open label trial

Primary objectives: Assess safety/tolerance, pk/pD, and explore dose-response of C2B8 in patients with relapsed/refractory CLL

Patient population: Active (progressing) CLL in patients with relapsed or refractory disease following a minimum of 1 prior chemotherapy regimen with acceptable baseline characteristics for performance status/life expectancy/absence of intercurrent illnesses; Platelet count =B375,000/mcl, HgB =B3=CA8, and =B3 30% lymphoma cells among nucleated= cells in
the marrow. Prednisone therapy is acceptable only if patients are on a stable dose =B2 20 mg for the month prior to study entry. Lymph counts 15,000-50,000/mcl (may be able to increase this value depending on investigator consultation).

Number of patients per dose level: 6. An additional 30 patients to be added at either one dose level below the MTD or at the optimum biologic dose.

Criteria for dose escalation: No intrapatient dose escalation, once 5/6 patients have completed one week of therapy without DLT, then next dose level can be opened.=20

Dose levels: 150,375, 500

Schedule of administration: Weekly x 4

Rate of infusion: 25 ml/hr then increase to 200 ml/hr as tolerated

MTD: defined as DLT in >1/3 or =B32/6 patients experienceDLT
DLT: bronchospasm, hypotension, angioedema (it occurs to me that these are not really dose limiting, but actually infusion-rate limiting- we should discuss this further)

Endpoints of interest: safety, trough drug levels, peripheral CD20+ counts, response as assessed by NCI criteria

Sites: MD Anderson, Long Island Jewish, Johns Hopkins. =20

John and I will be working on a draft for this protocol, which we will circulate to you at an early stage.=20

Best regards,=20
